Concentrations of Biogenic Amine Metabolites in Cerebrospinal Fluid from Normal Full Term and Premature Infants

Chia-Chang Hsieh, Wan-Ya Chang[2], and Ming-Tsuen Hsieh[3]

[1]*Department of Pediatrics, Veterans General Hospital-Taipei; National Yang-Ming University, School of Medicine,*
[2]*National Research Institute of Chinese Medicine,*
[3]*Institute of Chinese Pharmaceutical Sciences, China Medical College*

Abstract

To assess the maturation of central serotonin and catecholamine pathways between premature and full term babies, we measured homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) concentrations in lumbar CSF. Lumbar cerebrospinal fluid (CSF) was collected from 22 infants (8 premature and 14 at term), ranging in age from 1 day to 16 months old; all of them have no evidence of CNS disease by strict exclusions. In each specimen, concentrations of HVA, 5-HIAA, and MHPG, the stable acid metabolites of dopamine, serotonin and norepinephrine, were measured by using HPLC with electrochemical detection.

The mean of 5-HIAA in the premature group is significantly higher than full term group ($p < 0.05$, T-test). This result suggests that the premature have more serotonin activity. Our study also indicated a strong inverse correlation in infants between CSF 5-HIAA concentrations and age. This result revealed that age should be considered when interpreting results from studies on CSF levels of serotonin metabolites.

Key words: Neurotransmitter, Premature, HVA, 5-HIAA, MHPG

Correspondence to: Chia-Chang Hsieh
Department of Pediatrics,
Veterans General Hospital-Taipei,
Shih-Pai, Taipei, Taiwan, 11217, R.O.C.
TEL:(02)28757576

Introduction

Concentrations of monoamine metabolites in cerebrospinal fluid (CSF) reflect monoamine neurotransmitter metabolism in the central nervous system[1]. To assess the maturation of central serotonin and catecholamine pathways between premature and full term babies, some studies have been performed with measuring amine metabolites in CSF[2].

Previous studies revealed that 5-HIAA concentrations were similar in CSF from premature and full term babies[2,3]. But a study revealed that slightly higher 5-HIAA concentrations in CSF from premature infants compared with full term babies[4]. CSF HVA levels increased with maturity in some studies, and no significant differences were noted in CSF MHPG levels between premature and full term infants[2,5].

So we measured the levels of HVA, 5-HIAA and MHPG, stable metabolites of dopamine, serotonin and norepinephrine, in lumbar CSF from 22 infants, all of them have no evidence of neurological disease. We also calculate the correlation between ages and the three metabolites.

Material and Methods

During a period of 8 months, 53 lumbar CSF specimens were obtained from the Veterans General Hospital, Taipei, Taiwan, Department of Pediatrics. The most common reason for lumbar puncture was suspicion of infection. Lumbar puncture was done and lumbar CSF was obtained with the patient in the lateral decubitus position at radium times of day. Specimens containing visible amounts of red blood cells were eliminated from the study.

The 1 to 2 ml of CSF was collected into a plastic tube and was put into 4°C refrigerator immediately and then was stored at-70°C refrigerator within 24 hours until analysis. A previous study revealed that monoam-ine metabolites are stable at room temperature for more than 24 hours in lumbar CSF collected without antioxidants or preservatives[3].

These patients with meningitis, intracranial hemorrhage, hydrocephalus, asphyxia and other diseases which were suspected CNS involvement were excluded in this study. After careful reviews of the clinical and laboratory data, 22 of the original 53 individuals were found to have no evidence of suggestion of CNS disease. In these 22 patients, CSF fluid cultures were negative, and cell counts, protein and glucose values were within normal limits.

We divided these 22 lumbar CSF specimens into two groups, 14 full term infants (gestational age from 37 to 40 weeks) and 8 premature infants (gestational ages from 26 to 36 weeks). These 22 infants, aged from 1 day to 16 months, were 11 boys and 11 girls. HVA, 5-HIAA and MHPG were measured by using high performance liquid chromatography with electrochemical detection at the same time.

To analyze the difference of the premature group and the mature group, T-test was enplaned to compare the mean of MHPG, HVA and 5-HIAA between these two groups. The Pearson's correlation coefficient was used to find the connection among all variables.

Results

1. Effect between premature and full-term

CSF 5-HIAA levels are significantly higher ($p < 0.05$) in the premature group. (Fig. 1) Although the mean of CSF MHPG

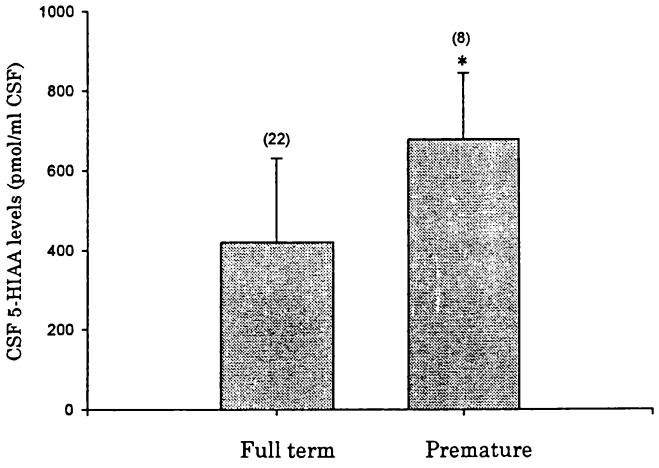

Fig 1. CSF 5-HIAA levels in the Full term and Premature infants. *P < 0.05 compared with the Full term group. The number of the tested infants are displayed in the parenthesis.

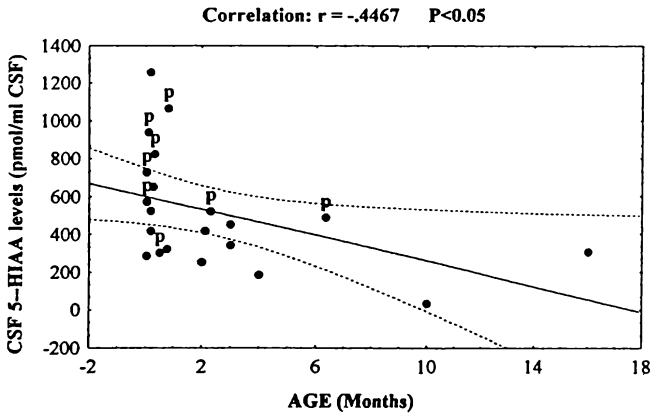

Fig 2. CSF 5-HIAA levels in the different ages. P: premature infants. The solid line presented as the linear regression line. The dash line presented as the 95% confidence interval.

Table 1. Lumbar CSF Concentration of HVA, 5-HIAA and MHPG in Full term and premature infants.

Groups	N	Concentration (pmol/ml)		
		5-HIAA	HVA	VMA
Full term	22	421.19 ± 60.65	627.66 ± 110.63	33.26 ± 7.12
Premature	8	678.62 ± 89.94*	458.26 ± 147.93	59.11 ± 11.84

Data are presented as mean ± SEM. N: numbers of infants. *P < 0.05 compared with the Full term group.

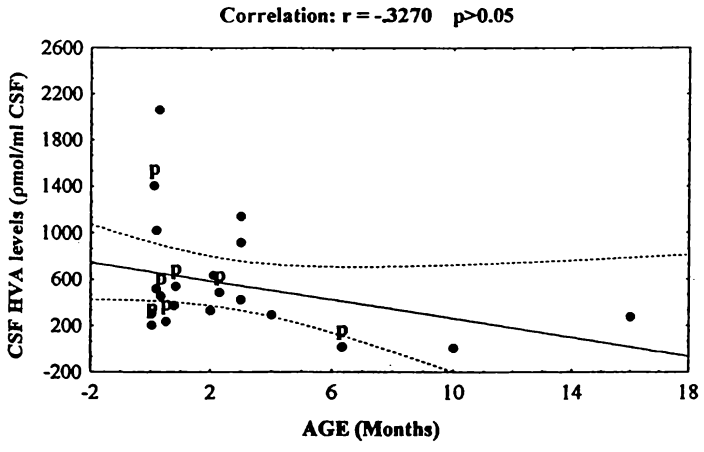

Fig 3. CSF HVA levels in the different ages. P: premature infants. The solid line presented as the linear regression line. The dash line presented as the 95% confidence interval.

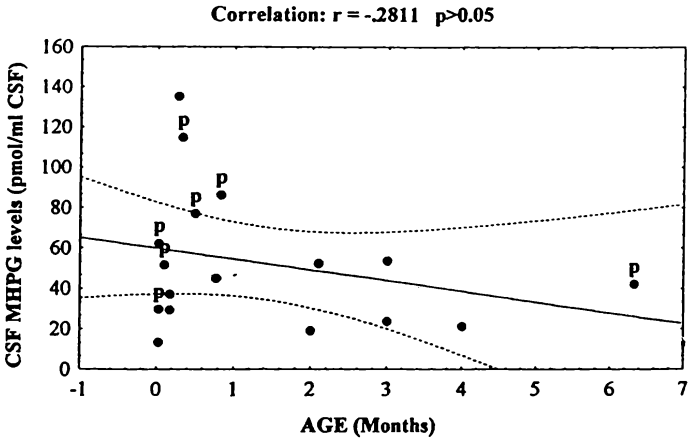

Fig 4. CSF MHPG levels in the different ages. P: premature infants. The solid line presented as the linear regression line. The dash line presented as the 95% confidence interval.

in the premature group is higher than that of full term, the difference is not statistically significant. Similarly, the mean of CSF HVA levels is higher in full term group but not significant. (Table 1)

2. Effect of age

5-HIAA has a significant inverse correlation with age ($r=-0.4$, $p < 0.05$). (Fig. 2) MHPG and HVA also have negative correlations with age, but have no significance. (Fig.3, Fig. 4)

Discussion

Although pediatric reference ranges have been studied for CSF monoamine metabolites, these findings have never been reported in pediatric population in Taiwan[6].

In our results, CSF 5-HIAA levels are significantly higher, CSF MHPG levels are higher and CSF HVA levels are lower in premature. A study revealed that slightly higher CSF 5-HIAA concentrations in premature infants, and it was compatible with our result[4]. But a study revealed that CSF 5-HIAA concentrations were similar between premature and full term babies[3]. In that study, 10 of the 12 premature infants were examined within the first month after birth. Differently, our patients' ages range from 1 day to 16 months. Therefore, age may be the factor that caused the different result.

Two studies revealed that CSF HVA levels increased with maturity[2,5]. Our results indicated that HVA was also higher in maturity, but with no significance. No significant difference was found in the levels of MHPG between premature and full term infants in previous studies[5]. In our study, there was also no significance in CSF MHPG levels between premature and mature, but higher in premature.

Our observation shows a statistically significant childhood age dependency for 5-HIAA levels in CSF. The inverse correlation was also observed between CSF HVA and MHPG concentrations and age, but with no significant correlation. The decrement in metabolite concentrations with age over the first few years of life had been observed in many published studies that have examined the effects of age[1,2,3,7,8].

This relationship should be considered when interpreting results from studies on CSF levels of these metabolites. However, it is unknown that the reasons for the higher CSF concentrations of HVA, 5-HIAA and MHPG in the newborns.

The reason for obtaining lumbar CSF in our cases was to rule out CNS infection. As a result, 6 of these individuals were febrile at the time of CSF collection. A comparison of the metabolite levels in age-paired febrile and afebrile subjects revealed no obvious differences in metabolite distribution[9]. Our study agrees with the result mentioned above. There were no sex differences for these values. (data not shown).

A study revealed no significant correlation between CSF metabolite concentrations and the time of day at which the specimen was withdrawn[3]. Our study agrees with the result mentioned above.

The means of 5-HIAA and MHPG are higher in premature group, whereas the mean of HVA is higher in full term group. These results suggest that the premature have more serotonin and norepiphrine synthesis and less dopamine activity. The present study also indicates that a rapid change occur in monoamine metabolite concentrations during the human perinatal period. These observations clearly emphasize the need for careful age-matching in the interpretation of CSF HVA, 5-HIAA, and MHPG

levels in infants and young children.

This study also provides valuable normal data for the interpretation of CSF monoamine metabolites in infants and children without neurological diseases. Wider application of similar CSF analysis in disorders that may disturbance dopamine or serotonin metabolism, for example: urea cycle and organic acid disorders, is like to be valuable in the future.

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正常足月兒與早產兒腦脊髓液中神經傳導物質代謝物濃度之研究

謝佳璋[1] 張婉雅[2] 謝明村[3]

[1]台北榮民總醫院 小兒部、國立陽明大學 醫學院
[2]國立中國醫藥研究所
[3]中國醫藥學院 中國藥學研究所

摘 要

本實驗目的旨在探討，正常足月兒與早產兒腦脊髓液中，神經傳導物質濃度之比較。共收集二十二例嬰兒，其中八例是早產兒，十四例是足月兒，抽取其腦脊髓液，並利用HPLC來測定其中神經傳導物質代謝產物濃度，例如HVA，5-HIAA及MHPG，其分別爲多巴胺、血清素及正腎上腺素之代謝產物。

實驗結果，早產兒腦脊髓液中5-HIAA濃度顯著高於足月兒，此結果顯示早產兒腦中有較高之血清素活性。本實驗亦顯示，腦脊髓液中5-HIAA濃度會隨著年齡之增加而減少，此結果指出，在研究腦脊髓液中血清素活性及其代謝產物時，必須將年齡之因素考慮在內。

關鍵詞：神經傳導物質、早產兒、HVA、5-HIAA、MHPG。